JAMA | Original Investigation

Association of Prior SARS-CoV-2 Infection With Risk of Breakthrough Infection Following mRNA Vaccination in Qatar

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IMPORTANCE The effect of prior SARS-CoV-2 infection on vaccine protection remains poorly understood.

OBJECTIVE To assess protection from SARS-CoV-2 breakthrough infection after mRNA vaccination among persons with vs without prior SARS-CoV-2 infection.

DESIGN, SETTING, AND PARTICIPANTS Matched-cohort studies in Qatar for the BNT162b2 (Pfizer-BioNTech) and mRNA-1273 (Moderna) vaccines. A total of 1 531 736 individuals vaccinated with either vaccine between December 21, 2020, and September 19, 2021, were followed up beginning 14 days after receiving the second dose until September 19, 2021.

EXPOSURES Prior SARS-CoV-2 infection and COVID-19 vaccination.

MAIN OUTCOMES AND MEASURES Incident SARS-CoV-2 infection, defined as a polymerase chain reaction (PCR)–positive nasopharyngeal swab regardless of reason for PCR testing or presence of symptoms. Cumulative incidence was calculated using the Kaplan-Meier estimator method.

RESULTS The BNT162b2-vaccinated cohort comprised 99 226 individuals with and 290 432 matched individuals without prior PCR-confirmed infection (median age, 37 years; 68% male). The mRNA-1273–vaccinated cohort comprised 58 096 individuals with and 169 514 matched individuals without prior PCR-confirmed infection (median age, 36 years; 73% male). Among BNT162b2-vaccinated persons, 159 reinfections occurred in those with and 2509 in those without prior infection 14 days or more after dose 2. Among mRNA-1273–vaccinated persons, 43 reinfections occurred in those with and 368 infections in those without prior infection. Cumulative infection incidence among BNT162b2-vaccinated individuals was an estimated 0.15% (95% CI, 0.12%-0.18%) in those with and 0.83% (95% CI, 0.79%-0.87%) in those without prior infection at 120 days of follow-up (adjusted hazard ratio for breakthrough infection with prior infection, 0.18 [95% CI, 0.15-0.21]; $P < .001$). Cumulative infection incidence among mRNA-1273–vaccinated individuals was an estimated 0.11% (95% CI, 0.08%-0.15%) in those with and 0.35% (95% CI, 0.32%-0.40%) in those without prior infection at 120 days of follow-up (adjusted hazard ratio, 0.35 [95% CI, 0.25-0.48]; $P < .001$). Vaccinated individuals with prior infection 6 months or more before dose 1 had statistically significantly lower risk for breakthrough infection than those vaccinated less than 6 months before dose 1 (adjusted hazard ratio, 0.62 [95% CI, 0.42-0.92]; $P = .02$ for BNT162b2 and 0.40 [95% CI, 0.18-0.91]; $P = .03$ for mRNA-1273 vaccination).

CONCLUSIONS AND RELEVANCE Prior SARS-CoV-2 infection was associated with a statistically significantly lower risk for breakthrough infection among individuals receiving the BNT162b2 or mRNA-1273 vaccines in Qatar between December 21, 2020, and September 19, 2021. The observational study design precludes direct comparisons of infection risk between the 2 vaccines.

JAMA. doi:10.1001/jama.2021.19623
Published online November 1, 2021.

Supplemental content

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The effect of prior SARS-CoV-2 infection on vaccine protection against future infection remains poorly understood.[1-3] Qatar launched COVID-19 immunization on December 21, 2020, first using the BNT162b2 (Pfizer-BioNTech) vaccine[4] and, 3 months later, adding the mRNA-1273 (Moderna) vaccine,[5] both following the US Food and Drug Administration-approved protocols.[6-8] As vaccination was scaled up, the country experienced 2 back-to-back SARS-CoV-2 waves from January through June 2021, which were dominated by the Alpha[9] (B.1.1.7) and Beta[9] (B.1.351) variants[6,7,10-12] (eFigure 1 and eMethods in the Supplement). Appreciable community transmission of the Delta[9] (B.1.617.2) variant was first detected toward the end of March 2021, and by summer 2021, Delta had become the dominant variant.[10-12] This provided an opportunity to assess whether persons vaccinated after a prior SARS-CoV-2 infection had a lower incidence of breakthrough infection than those vaccinated without prior infection.

Key Points

Question Are persons vaccinated after SARS-CoV-2 infection better protected against breakthrough infection than those vaccinated without prior infection?

Findings In this cohort study of 1 531 736 mRNA-vaccinated individuals in Qatar, prior SARS-CoV-2 infection was associated with a statistically significant reduced hazard of breakthrough infection among recipients of both the BNT162b2 (Pfizer-BioNTech) (adjusted hazard ratio, 0.62) and the mRNA-1273 (Moderna) vaccines (adjusted hazard ratio, 0.40).

Meaning Prior SARS-CoV-2 infection was associated with a lower risk for breakthrough infection among persons receiving the SARS-CoV-2 mRNA vaccines; however, the observational study design precludes direct comparison of infection risk between the 2 vaccines.

Methods

This retrospective study was approved by the Hamad Medical Corporation and Weill Cornell Medicine-Qatar Institutional Review Boards with waiver of informed consent because only routinely collected data were used.

Participants

This study was conducted in the resident population of Qatar and leveraged the national, federated databases at Hamad Medical Corporation, the main public health care provider and the nationally designated provider for all COVID-19 health care needs. These databases were constructed to capture all SARS-CoV-2–related data along with related demographic details since the start of the epidemic, including all records of polymerase chain reaction (PCR) testing, COVID-19 hospitalizations, COVID-19 vaccinations, SARS-CoV-2 infection severity classification per World Health Organization (WHO) guidelines,[13] and COVID-19 deaths, also assessed per WHO guidelines.[14] Every PCR test conducted in Qatar, regardless of location (eg, outpatient clinic, drive-through testing site, or hospital), is classified on the basis of symptoms and the reason for testing (clinical symptoms, contact tracing, random testing campaigns [surveys], individual requests, routine health care testing, pretravel, and at port of entry).

Association between prior infection and acquisition of infection after vaccination was investigated using 2 retrospective, matched-cohort studies. The eligible study population included all BNT162b2-vaccinated and mRNA-1273-vaccinated individuals in the Hamad Medical Corporation database between December 21, 2020, and September 19, 2021. We compared incidence of documented SARS-CoV-2 infection 14 days or more after the second vaccine dose in the cohort of individuals who had experienced PCR-confirmed infection before vaccination vs incidence among those who had no record of a prior infection for both the BNT162b2 and mRNA-1273 vaccine cohorts.

Every individual vaccinated with BNT162b2 or mRNA-1273 was classified based on prior infection status (with or without PCR-positive nasopharyngeal swab before the first dose of vaccination). Individuals were exact matched based on prior infection status in a 1:3 ratio by sex, 5-year age group, nationality, and calendar week of first vaccine dose to control for differences in exposure risk[15,16] and variant exposure.[6,7,10-12] Sex, age, and nationality were based on the recorded entries in the national registry of the national health care system, but other variables, such as occupation, were not available to the study investigators. Only matched samples were included in the analysis. By virtue of having many more vaccinated individuals with no prior infection than vaccinated individuals with prior infection, it was generally possible to find exact matches.

An additional analysis was conducted to compare the incidence of breakthrough infection in the cohort of individuals with a prior PCR-confirmed infection 6 months or more before dose 1 vs a matched cohort of individuals with a prior PCR-confirmed infection less than 6 months before dose 1. This analysis was conducted to assess the association between timing of boosting of natural immunity through vaccination and incidence of breakthrough infection. This analysis was done for both vaccines. Individuals were exact matched in a 1:1 ratio by sex, 5-year age group, nationality, and calendar week of first vaccine dose.

For each individual in the study, follow-up lasted from 14 days after the second dose to the earliest occurrence of any of the following: a PCR-positive nasopharyngeal swab, all-cause death, or end-of-study censoring.

Exposure

Exposure was a documented SARS-CoV-2 infection any time prior to first dose of BNT162b2 or mRNA-1273 COVID-19 vaccine. Documented SARS-CoV-2 infection was defined as a PCR-positive nasopharyngeal swab regardless of the reason for PCR testing or presence of symptoms.

Outcomes

The primary outcome was documented SARS-CoV-2 (breakthrough) infection 14 days or more after the second dose of

either the BNT162b2 or mRNA-1273 vaccine. Fourteen days was chosen because earlier evidence indicated that BNT162b2-vaccinated or mRNA-1273–vaccinated individuals reach full vaccine-induced immunity within this time.[4,5,8]

Severe,[13] critical,[13] or fatal[14] COVID-19 breakthrough disease was examined as an additional exploratory outcome. Classification of COVID-19 case severity (acute-care hospitalizations),[13] criticality (intensive care unit [ICU] hospitalizations),[13] and fatality[14] followed WHO guidelines, and assessments were made by trained medical personnel using individual medical record reviews (eMethods in the Supplement).

Statistical Analyses

Descriptive statistics (frequency distributions and measures of central tendency) were used to characterize study samples. Standardized mean differences were used to compare groups, with a standardized mean difference less than 0.1 indicating adequate matching.[17] The Kaplan-Meier estimator method[18] was used to estimate the cumulative incidence of infection. Cumulative incidence of infection was defined as the proportion of individuals at risk who were identified with a breakthrough infection during follow-up among all eligible individuals in each cohort. The log-rank test was applied to assess equality of failure functions. Standard errors of failure functions were used to derive the 95% CIs of the absolute difference in cumulative incidence at different follow-up times. Incidence rates of infection were calculated by dividing the number of breakthrough infection cases identified during follow-up by the number of person-weeks contributed by all eligible individuals in the cohort. Incidence rates and corresponding 95% CIs were estimated using a Poisson log-likelihood regression model with the Stata version 17.0 *stptime* command.[19]

Follow-up person-time was calculated from the day each individual completed 14 days after the second vaccine dose up to the infection swab, all-cause death, or end-of-study censoring (September 19, 2021). The hazard ratios (HR) and corresponding 95% CIs were calculated using Cox regression adjusted for the matching factors with the Stata version 17.0 *stcox* command.[19] Schoenfeld residuals and log-log plots were used to test the proportional-hazards assumption, which was generally met at nearly all time points, and subgroup analyses were performed to estimate adjusted HRs stratified by month of follow-up.

The analyzed national databases had no missing information for PCR testing outcomes, the matching factors, and severe, critical, or fatal COVID-19 disease. In all analyses, 2-sided $P < .05$ indicated statistical significance. Statistical analyses were conducted in Stata/SE version 17.0.[19]

Results

Study Population

A total of 1 531 736 eligible BNT162b2-vaccinated and mRNA-1273–vaccinated individuals were identified. Baseline characteristics of each vaccine cohort are shown in eTable 1 in the Supplement. There were small differences in median age and sex, but large differences in age distribution, nationality, and calendar month of dose 1 reflecting introduction of the mRNA-1273 vaccine 3 months after BNT162b2 (eFigure 1 in the Supplement), and a phased vaccine rollout prioritizing frontline health care workers, persons with severe or multiple chronic conditions, select occupational groups such as teachers, and age, all in context of associations with age, nationality, and occupation.[8,15,20-22] Qatar has unusually young, diverse demographics, in that only 9% of its residents are 50 years or older, and 89% are expatriates residing in Qatar on work visas from more than 150 countries, of whom most are male.[15,23]

A median of 21 days (IQR, 21-22) elapsed between the first and second BNT162b2 doses; 97.4% of individuals received their second dose 30 days or less after their first dose. A median of 28 days (IQR, 28-31) elapsed between the first and second mRNA-1273 doses; 74.9% of individuals received their second dose 30 days or less after their first dose.

Of 963 899 BNT162b2-vaccinated individuals, 100 486 had prior PCR-confirmed infection; 99 226 were matched to 290 432 BNT162b2-vaccinated individuals with no record of prior infection (**Figure 1**). Proportions who had a PCR test done during follow-up were 45.0% and 41.8% among those with and without a prior infection, respectively.

Before matching, those with and without prior infection were well balanced in median age, age distribution, and sex, but with differences by nationality and calendar month of dose 1, which balanced with matching (**Table 1**).

Of 564 906 mRNA-1273–vaccinated individuals, 58 987 had prior PCR-confirmed infection; 58 096 were matched to 169 514 mRNA-1273–vaccinated individuals with no record of prior infection (Figure 1). Proportions who had a PCR test done during follow-up were 32.1% and 28.5% among those with and without prior infection, respectively.

Before matching, those with and without prior infection were well balanced in median age, age distribution, and sex, but with differences by nationality and calendar month of dose 1, which balanced with matching (**Table 2**).

Infection Incidence Among BNT162b2-Vaccinated Individuals

Among BNT162b2-vaccinated people with prior infection (Figure 1), 159 reinfections occurred 14 days or more after dose 2 at a median follow-up of 55 days (IQR, 18-108). One progressed to severe COVID-19 disease and none to critical or fatal COVID-19 disease.

Among BNT162b2-vaccinated people without prior infection, 2509 infections occurred 14 days or more after dose 2 at a median follow-up of 60 days (IQR, 25-113). Twenty-six progressed to severe COVID-19 disease, 2 to critical disease, and 0 to COVID-19 death.

Most breakthrough infections occurred during times when the Beta or Delta variants dominated (eFigure 1 and eMethods in the Supplement). There were differences in age, nationality, and particularly calendar month of dose 1 between those with or without breakthrough infection. Those with breakthrough infection tended to have received their vaccination earlier (eTable 2 in the Supplement).

Cumulative infection incidence among BNT162b2-vaccinated individuals was an estimated 0.15% (95% CI,

Figure 1. Development of Cohorts in a Study of SARS-CoV-2 Infections After Vaccination With and Without Prior Infection

PCR indicates polymerase chain reaction.

[a] Individuals were exact matched based on infection status with no replacement allowed on a 1:3 ratio by sex, 5-year age group, nationality, and calendar week of first vaccine dose. Matching did not exactly reach 1:3 ratio because of low frequency in older age categories and for specific nationalities.

[b] Severe disease included hospitalization that did not require intensive care; critical disease included patients admitted to the intensive care unit.

[c] Deaths were not related to COVID-19.

Table 1. Demographic Characteristics of Cohorts That Received the BNT162b2 Vaccine

Characteristic	No. (%)					
	Full cohorts			Matched cohorts[a]		
	Individuals with a prior PCR-confirmed infection	Individuals with no prior PCR-confirmed infection	SMD[b]	Individuals with a prior PCR-confirmed infection	Individuals with no prior PCR-confirmed infection	SMD[b]
No.	100 486	787 821		99 226	290 432	
Total follow-up time, person-weeks	1 608 209	13 948 047		1 590 926	4 645 689	
Age, median (IQR), y	37 (29-44)	37 (29-46)	0.06[c]	37 (29-44)	37 (29-44)	0.009[c]
Age group, y						
<20	10 257 (10.2)	83 043 (10.5)	0.10	10 158 (10.2)	29 891 (10.3)	0.01
20-29	15 020 (15.0)	114 120 (14.5)		14 804 (14.9)	43 196 (14.9)	
30-39	36 567 (36.4)	262 939 (33.4)		36 315 (36.6)	107 458 (37.0)	
40-49	23 193 (23.1)	183 444 (23.3)		22 920 (23.1)	66 890 (23.0)	
50-59	10 802 (10.8)	93 616 (11.9)		10 579 (10.7)	30 433 (10.5)	
60-69	3683 (3.7)	38 760 (4.9)		3553 (3.6)	10 071 (3.5)	
≥70	964 (1.0)	11 899 (1.5)		897 (0.9)	2493 (0.9)	
Sex						
Male	68 186 (67.9)	505 040 (64.1)	0.08	67 520 (68.1)	198 356 (68.3)	0.005
Female	32 300 (32.1)	282 781 (35.9)		31 706 (32.0)	92 076 (31.7)	
Nationality[d]						
Bangladeshi	8009 (8.0)	70 622 (9.0)	0.18	7989 (8.1)	23 719 (8.2)	0.03
Egyptian	6340 (6.3)	51 232 (6.5)		6328 (6.4)	18 770 (6.5)	
Filipino	10 484 (10.4)	78 927 (10.0)		10 459 (10.5)	30 255 (10.4)	
Indian	24 560 (24.4)	171 630 (21.8)		24 549 (24.7)	73 426 (25.3)	
Nepalese	8180 (8.1)	42 358 (5.4)		8141 (8.2)	24 017 (8.3)	
Pakistani	4133 (4.1)	28 897 (3.7)		4110 (4.1)	12 075 (4.2)	
Qatari	16 943 (16.9)	136 882 (17.4)		16 938 (17.1)	50 288 (17.3)	
Sri Lankan	2988 (3.0)	21 653 (2.8)		2971 (3.0)	8819 (3.0)	
Sudanese	2545 (2.5)	17 812 (2.3)		2522 (2.5)	7271 (2.5)	
Other nationalities[e]	16 304 (16.2)	167 808 (21.3)		15 219 (15.3)	41 792 (14.4)	
Calendar month of dose 1						
December	215 (0.2)	5304 (0.7)	0.31	203 (0.2)	567 (0.2)	0.02
January	3114 (3.1)	42 296 (5.4)		3027 (3.1)	8703 (3.0)	
February	9613 (9.6)	115 107 (14.6)		9529 (9.6)	27 881 (9.6)	
March	17 727 (17.6)	184 279 (23.4)		17 607 (17.7)	52 515 (18.1)	
April	19 988 (19.9)	148 557 (18.9)		19 811 (20.0)	58 793 (20.2)	
May	33 681 (33.5)	186 681 (23.7)		33 357 (33.6)	96 925 (33.4)	
June	10 256 (10.2)	69 866 (8.9)		10 067 (10.2)	29 402 (10.1)	
July	4380 (4.4)	26 589 (3.4)		4216 (4.3)	11 748 (4.1)	
August	1512 (1.5)	9142 (1.2)		1409 (1.4)	3898 (1.3)	

Abbreviations: PCR, polymerase chain reaction; SMD, standardized mean difference.

[a] Cohorts were exact matched in a 1:3 ratio by sex, 5-year age group, nationality, and calendar week of first vaccine dose.

[b] SMD is the difference in the mean of a covariate between groups divided by the pooled SD. An SMD less than 0.1 indicates adequate matching.

[c] SMD is for the mean difference between groups divided by the pooled SD.

[d] Nationalities were chosen to represent the most numerous groups in the population of Qatar.

[e] Individuals who received the BNT162b2 vaccine in Qatar comprised 133 other nationalities in the full cohort of individuals with a prior PCR-confirmed infection, 184 other nationalities in the full cohort of individuals with no prior PCR-confirmed infection, 102 other nationalities in the matched cohort of individuals with a prior PCR-confirmed infection, and 102 other nationalities in the matched cohort of individuals with no prior PCR-confirmed infection.

0.12%-0.18%) in those with and 0.83% (95% CI, 0.79%-0.87%) in those without prior infection at 120 days (**Figure 2**A; eFigure 2A in the Supplement). Cumulative infection incidence appeared to accelerate among those without prior infection after the 110th day of follow-up.

Overall infection incidence rate among BNT162b2-vaccinated individuals was an estimated 1.00 (95% CI, 0.86-1.17) and 5.40 (95% CI, 5.19-5.26) per 10 000 person-weeks among those with and without prior infection, respectively (adjusted HR for breakthrough infection with prior infection,

Table 2. Demographic Characteristics of Cohorts That Received the mRNA-1273 Vaccine

Characteristic	No. (%)					
	Full cohorts			Matched cohorts[a]		
	Individuals with a prior PCR-confirmed infection	Individuals with no prior PCR-confirmed infection	SMD[b]	Individuals with a prior PCR-confirmed infection	Individuals with no prior PCR-confirmed infection	SMD[b]
No.	58 987	426 574		58 096	169 514	
Total follow-up time, person-weeks	694 259	5 482 776		685 351	2 008 963	
Age, median (IQR), y	36 (31-44)	36 (31-44)	0.01[c]	36 (31-44)	36 (31-44)	0.01[c]
Age group, y						
<20	545 (0.9)	4975 (1.2)	0.05	512 (0.9)	1361 (0.8)	0.02
20-29	10 189 (17.3)	78 841 (18.5)		10 052 (17.3)	29 446 (17.4)	
30-39	24 973 (42.3)	172 736 (40.5)		24 771 (42.6)	73 013 (43.1)	
40-49	15 618 (26.5)	115 286 (27.0)		15 440 (26.6)	45 034 (26.6)	
50-59	6079 (10.3)	43 817 (10.3)		5918 (10.2)	16 915 (10.0)	
60-69	1328 (2.3)	9082 (2.1)		1206 (2.1)	3259 (1.9)	
≥70	255 (0.4)	1837 (0.4)		197 (0.3)	486 (0.3)	
Sex						
Male	42 653 (72.3)	302 456 (70.9)	0.03	42 180 (72.6)	123 872 (73.1)	0.01
Female	16 334 (27.7)	124 118 (29.1)		15 916 (27.4)	45 642 (26.9)	
Nationality[d]						
Bangladeshi	6504 (11.0)	61 115 (14.3)	0.15	6491 (11.2)	19 407 (11.5)	0.04
Egyptian	3432 (5.8)	25 629 (6.0)		3420 (5.9)	10 127 (6.0)	
Filipino	7922 (13.4)	53 292 (12.5)		7899 (13.6)	22 605 (13.3)	
Indian	18 432 (31.3)	120 516 (28.3)		18 426 (31.7)	55 155 (32.5)	
Nepalese	5817 (9.9)	33 972 (8.0)		5803 (10.0)	17 226 (10.2)	
Pakistani	3184 (5.4)	21 009 (4.9)		3164 (5.5)	9174 (5.4)	
Qatari	1652 (2.8)	12 564 (3.0)		1639 (2.8)	4705 (2.8)	
Sri Lankan	2565 (4.4)	18 631 (4.4)		2551 (4.4)	7593 (4.5)	
Sudanese	1341 (2.3)	8729 (2.1)		1329 (2.3)	3777 (2.2)	
Other nationalities[e]	8138 (13.8)	71 117 (16.7)		7374 (12.7)	19 745 (11.7)	
Calendar month of dose 1						
December	0	2 (0.0005)	0.23	0	0	0.02
January	0	14 (0.003)		0	0	
February	88 (0.2)	851 (0.2)		80 (0.1)	179 (0.1)	
March	8301 (14.1)	83 474 (19.6)		8218 (14.2)	24 511 (14.5)	
April	16 539 (28.0)	142 424 (33.4)		16 379 (28.2)	48 426 (28.6)	
May	14 833 (25.2)	80 726 (18.9)		14 613 (25.2)	42 313 (25.0)	
June	7892 (13.4)	46 696 (11.0)		7715 (13.3)	22 146 (13.1)	
July	9154 (15.5)	57 672 (13.5)		8965 (15.4)	25 573 (15.1)	
August	2180 (3.7)	14 715 (3.5)		2126 (3.7)	6366 (3.8)	

Abbreviations: PCR, polymerase chain reaction; SMD, standardized mean difference.

[a] Cohorts were exact matched in a 1:3 ratio by sex, 5-year age group, nationality, and calendar week of first vaccine dose.

[b] SMD is the difference in the mean of a covariate between groups divided by the pooled SD. An SMD less than 0.1 indicates adequate matching.

[c] SMD is for the mean difference between groups divided by the pooled SD.

[d] Nationalities were chosen to represent the most numerous groups in the population of Qatar.

[e] Individuals who received the mRNA-1273 vaccine in Qatar comprised 114 other nationalities in the full cohort of individuals with a prior PCR-confirmed infection, 163 other nationalities in the full cohort of individuals with no prior PCR-confirmed infection, 85 other nationalities in the matched cohort of individuals with a prior PCR-confirmed infection, and 85 other nationalities in the matched cohort of individuals with no prior PCR-confirmed infection.

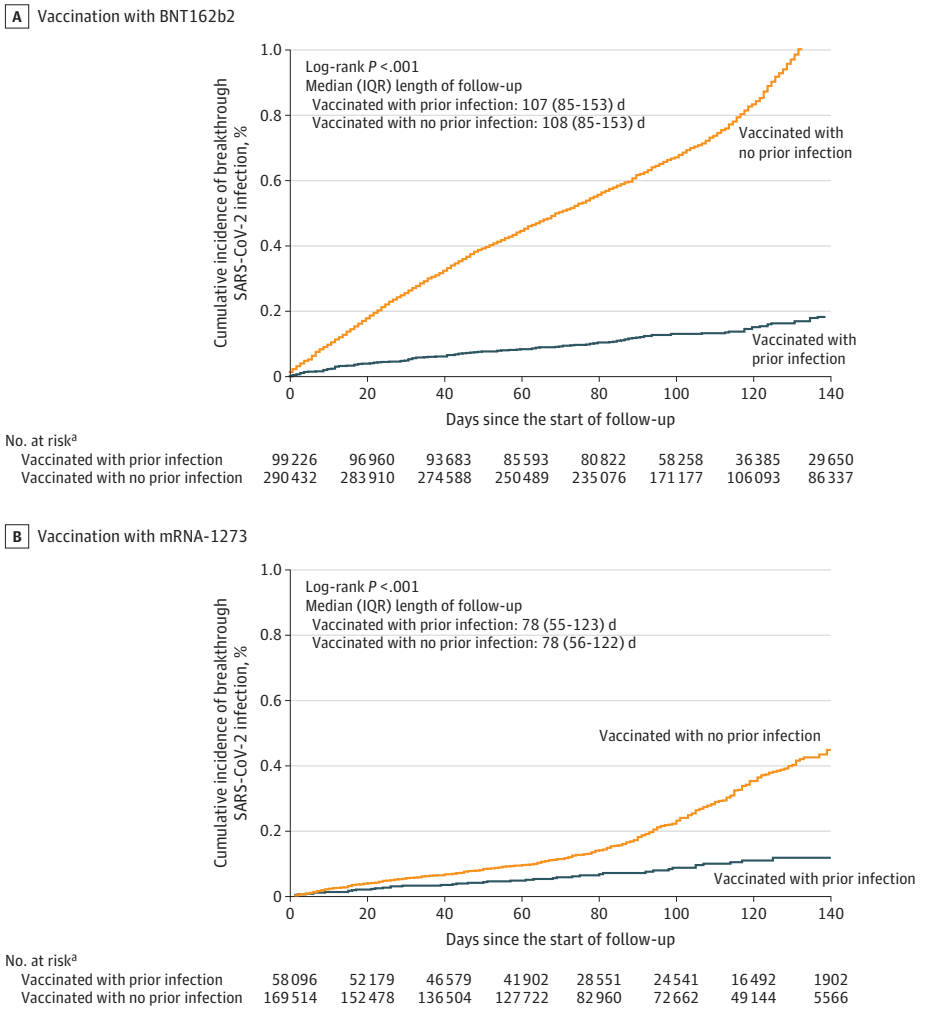
0.18 [95% CI, 0.15-0.21]; $P < .001$). The adjusted HR by month of follow-up appeared stable over time after dose 2 (**Table 3**).

Infection Incidence Among mRNA-1273–Vaccinated Individuals

Among mRNA-1273–vaccinated people with prior infection (Figure 1), 43 reinfections occurred 14 days or more after dose 2 at a median follow-up of 46 days (IQR, 16-81). None progressed to severe, critical, or fatal COVID-19 disease.

Among mRNA-1273–vaccinated people without prior infection, 368 infections occurred 14 days or more after dose 2 at a median follow-up of 77 days (IQR, 30-104). One progressed to severe COVID-19 disease and none to critical or fatal COVID-19 disease.

Figure 2. Cumulative Infection Incidence Among Matched Cohorts of BNT162b2-Vaccinated and mRNA-1273–Vaccinated Individuals With and Without Prior Infection



[a] See eFigure 2 in the Supplement for extended follow-up of the BNT162b2 cohort.

Most breakthrough infections occurred during times when the Beta or Delta variants dominated (eFigure 1 and eMethods in the Supplement). There were differences in age, nationality, and particularly calendar month of dose 1 between those with or without breakthrough infection. Those with breakthrough infection tended to have received their vaccination earlier (eTable 2 in the Supplement).

Cumulative infection incidence among mRNA-1273-vaccinated individuals was an estimated 0.11% (95% CI, 0.08%-0.15%) in those with and 0.35% (95% CI, 0.32%-0.40%) in those without prior infection at 120 days (Figure 2B; eFigure 2B in the Supplement). Cumulative infection incidence appeared to accelerate among those without prior infection after the 80th day of follow-up.

Overall infection incidence rate among mRNA-1273-vaccinated individuals was an estimated 0.63 (95% CI, 0.47-0.85) and 1.83 (95% CI, 1.65-2.03) per 10 000 person-weeks in those with and without prior infection, respectively (adjusted HR for breakthrough infection with prior infection, 0.35 (95% CI, 0.25-0.48); $P < .001$). The adjusted HR by month of follow-up appeared to decline over time after dose 2 (Table 3).

Infection Incidence by Time Interval Between Prior Infection and Vaccination

Of 100 486 BNT162b2-vaccinated individuals with prior infection, 50 285 had the prior infection 6 months or more and 50 201 had the prior infection less than 6 months before their first vaccine dose (eFigure 3 in the Supplement). Of the 50 285 individuals whose prior infection was 6 months or more before their first dose, 29 582 were matched to 29 582 individuals whose prior infection occurred less than 6 months before their first dose.

Cumulative infection incidence among BNT162b2-vaccinated individuals with prior infection was an estimated 0.13% (95% CI, 0.09%-0.19%) when infection was 6 months or more and 0.20% (95% CI, 0.15%-0.26%) when less than 6 months before dose 1, at 120 days of follow-up (eFigure 4 in the Supplement).

Table 3. Adjusted Hazard of Breakthrough Infection by Month of Follow-up in Matched Cohorts of Vaccinated Individuals With vs Without Prior Infection

Follow-up time, mo	Vaccinated with prior infection[a]		Vaccinated with no prior infection[a]		Absolute difference of cumulative incidence (95% CI)[b]	Adjusted hazard ratio (95% CI)[c]	*P* value
	No.	Cumulative incidence (95% CI)	No.	Cumulative incidence (95% CI)			
BNT162b2							
1	96 125	0.05 (0.03 to 0.06)	281 488	0.24 (0.23 to 0.26)	0.19 (0.16 to 0.22)	0.19 (0.14 to 0.26)	<.001
2	85 702	0.08 (0.07 to 0.10)	250 851	0.43 (0.41 to 0.46)	0.35 (0.32 to 0.38)	0.19 (0.13 to 0.27)	<.001
3	70 718	0.12 (0.10 to 0.14)	203 501	0.60 (0.57 to 0.63)	0.48 (0.45 to 0.51)	0.21 (0.14 to 0.31)	<.001
4	37 004	0.15 (0.12 to 0.18)	107 822	0.81 (0.78 to 0.85)	0.66 (0.62 to 0.70)	0.13 (0.08 to 0.22)	<.001
5	27 231	0.22 (0.18 to 0.27)	79 210	1.20 (1.15 to 1.26)	0.98 (0.91 to 1.05)	0.19 (0.12 to 0.29)	<.001
≥6	1235	0.31 (0.23 to 0.41)	3409	2.00 (1.82 to 2.18)	1.69 (1.48 to 1.88)	0.16 (0.09 to 0.30)	<.001
mRNA-1273							
1	47 976	0.03 (0.02 to 0.05)	140 573	0.05 (0.04 to 0.07)	0.02 (-0.008 to 0.05)	0.62 (0.37 to 1.03)	.06
2	42 349	0.05 (0.03 to 0.07)	124 044	0.09 (0.08 to 0.11)	0.04 (0.01 to 0.07)	0.38 (0.17 to 0.83)	.02
3	25 144	0.07 (0.05 to 0.10)	74 323	0.17 (0.15 to 0.20)	0.10 (0.07 to 0.13)	0.32 (0.16 to 0.67)	.002
4	296	0.12 (0.09 to 0.17)	794	0.57 (0.37 to 0.89)	0.45 (0.19 to 0.71)	0.20 (0.10 to 0.37)	<.01

[a] Cohorts were exact matched in a 1:3 ratio by sex, 5-year age group, nationality, and calendar week of first vaccine dose.

[b] Standard errors of failure functions were used to derive the 95% CIs of the absolute difference in cumulative incidence at different follow-up times.

[c] Hazard ratios were adjusted by sex, 5-year age group, 10 nationality groups (described in Tables 1 and 2), and calendar week of first vaccine dose.

Overall infection incidence rate among BNT162b2-vaccinated individuals with prior infection was an estimated 0.85 (95% CI, 0.62-1.16) and 1.41 (95% CI, 1.10-1.80) per 10 000 person-weeks in those whose infection was 6 months or more vs less than 6 months before their first vaccine dose, respectively (adjusted HR for breakthrough infection with prior infection 6 months or more before first vaccine dose, 0.62 [95% CI, 0.42-0.92]; *P* = .02).

Of 58 987 mRNA-1273-vaccinated individuals with prior infection, 27 388 had the prior infection 6 months or more and 31 599 individuals had the prior infection less than 6 months before their first vaccine dose (eFigure 3 in the Supplement). Of the 27 388 individuals whose prior infection was 6 months or more before their first dose, 16 873 were matched to 16 873 individuals who had the prior infection less than 6 months before their first dose.

Cumulative infection incidence among mRNA-1273-vaccinated individuals with prior infection was an estimated 0.05% (95% CI, 0.02%-0.11%) when infection was 6 months or more before dose 1 and 0.20% (95% CI, 0.12%-0.31%) when it was less than 6 months before dose 1, at 120 days of follow-up (eFigure 4 in the Supplement).

Overall infection incidence rate among mRNA-1273-vaccinated individuals with prior infection was an estimated 0.40 (95% CI, 0.20-0.80) and 1.00 (95% CI, 0.65-1.55) per 10 000 person-weeks among those whose infection was 6 months or more vs less than 6 months before their first vaccine dose, respectively (adjusted HR for breakthrough infection with prior infection 6 months or more before first vaccine dose, 0.40 [95% CI, 0.18-0.91]; *P* = .03).

Discussion

In this cohort study, prior SARS-CoV-2 infection was associated with a lower risk for breakthrough infection among individuals receiving the BNT162b2 or mRNA-1273 vaccines. Although the 2 vaccines were found earlier in Qatar to be highly effective against the Alpha, Beta, and Delta variants,[6,7,24-26] prior infection among those vaccinated—a hybrid of natural and vaccine immunity—appeared to be associated with additional reduction in breakthrough infection.

Incidence of breakthrough infection also appeared to accelerate with time after the second dose among those with no prior infection, perhaps reflecting waning of vaccine-induced immunity over time, as indicated recently in Qatar.[8] Incidence of breakthrough infection was statistically significantly lower among those vaccinated more than 6 months compared with less than 6 months after prior infection. Evidence suggests that mRNA-1273 induces higher neutralizing antibody titers than BNT162b2.[27] The interval between doses is 1 week longer for mRNA-1273, and evidence suggests that a longer dose interval is associated with improved protection after receiving the second dose.[28] The mRNA-1273 vaccine dose is also larger than BNT162b2.[4,5] These factors could explain some of the observed differences in incidence of breakthrough infection for those vaccinated by these 2 vaccines.

The strengths of this study include the use of very large cohorts of BNT162b2-vaccinated and mRNA-1273-vaccinated persons that were followed up for several months in a setting where all PCR-confirmed infections are centrally tracked and recorded at the national level.

Limitations

This study has several limitations. First, prior infection was identified based on a record of a PCR-positive result, thereby missing those who may have been infected but were unaware of their infection or who did not seek testing to document the infection. Misclassification of prior infection status may have underestimated the association of prior infection with observed outcomes.

Second, depletion of the cohorts with prior infection by COVID-19 mortality at time of prior infection may have biased these cohorts toward healthier individuals with stronger immune responses. However, COVID-19 mortality has been low in Qatar's predominantly young and working-age population.[15,29]

Third, the BNT162b2-vaccinated cohort was larger than that of the mRNA-1273–vaccinated cohort and was followed up for a longer time. However, both cohorts were very large, leading to results with statistical precision. The results were also presented at different times of follow-up to allow comparisons. Both vaccines were mass distributed across the country's neighborhoods/areas and population social substrata. People were generally vaccinated using the vaccine that was available at the time of the vaccination. Infection incidence was also broadly distributed across the country's neighborhoods/areas and population social substrata. Matching was implemented to control for differences in exposure risk[15,16] and variant exposure.[6,7,10-12] Therefore, it is not likely that observed differences between the 2 vaccines could be explained by clustering of vaccination or infection in specific geographies or social strata.

Fourth, vaccinated cohorts predominantly included working-age adults; therefore, results may not necessarily be generalizable to other population groups, such as children or elderly individuals.

Fifth, matching was done for age, sex, nationality, and calendar week of the first vaccine dose, and could not be done for other factors, such as comorbidities, because these were not available to study investigators. However, matching by age and sex may have served as a proxy given that comorbidities are associated with older age and may differ between women and men. Matching by nationality may have captured some of the occupational risk, given the distribution of the labor force in Qatar.[20-22] The number of persons with severe or multiple chronic conditions is small in Qatar. The national list of vaccine prioritization included only 19 800 individuals of all age groups with serious comorbid conditions to be prioritized in the first phase of vaccine roll-out.

Sixth, as an observational study, there remains potential for unmeasured residual confounding that could not be controlled for.

Conclusions

Prior SARS-CoV-2 infection was associated with a statistically significantly lower risk for breakthrough infection among individuals receiving the BNT162b2 or mRNA-1273 vaccines in Qatar between December 21, 2020, and September 19, 2021. The observational study design precludes direct comparisons of infection risk between the 2 vaccines.

ARTICLE INFORMATION

Accepted for Publication: October 15, 2021.

Published Online: November 1, 2021. doi:10.1001/jama.2021.19623

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Conflict of Interest Disclosures: Dr Butt reported receiving institutional grant funding from Gilead Sciences unrelated to the current study. No other disclosures were reported.

Funding/Support: Qatar Genome Programme provided funding for the viral genome sequencing. Support was provided by the Biomedical Research Program; the Biostatistics, Epidemiology, and Biomathematics Research Core; and the Genomics Core, all at Weill Cornell Medicine–Qatar, as well as from the Ministry of Public Health and Hamad Medical Corporation to facilitate the conduct of this study.

Role of the Funder/Sponsor: The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Disclaimer: Statements made herein are solely the responsibility of the authors.

Additional Contributions: We acknowledge the many individuals at Hamad Medical Corporation, the Qatar Ministry of Public Health, the Primary Health Care Corporation, Sidra Medicine, and the Qatar Biobank for their efforts and contributions to make this study possible.

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